



Journal of Cystic Fibrosis 12 (2013) 599–603

Journal of **Cystic  
Fibrosis**  
www.elsevier.com/locate/jcf

## Original Article

# Effects of ivacaftor on severely ill patients with cystic fibrosis carrying a G551D mutation☆

Helge Hebestreit<sup>a,\*</sup>, Annette Sauer-Heilborn<sup>b</sup>, Rainald Fischer<sup>c</sup>,  
Manfred Käding<sup>d</sup>, Jochen G. Mainz<sup>e</sup>

<sup>a</sup> Universitäts-Kinderklinik, Würzburg, Germany

<sup>b</sup> Klinik für Pneumologie, Medizinische Hochschule Hannover, Germany

<sup>c</sup> Medizinische Klinik Innenstadt, München, Germany

<sup>d</sup> Poliklinik Chemnitz GmbH, Kinderarztpraxis, Germany

<sup>e</sup> Department of Paediatrics, CF-Centre, Jena University Hospital, Germany

Received 18 February 2013; received in revised form 3 May 2013; accepted 3 May 2013

Available online 10 June 2013

## Abstract

**Background:** Recently, ivacaftor, a CFTR-potentiator, has been shown to be effective and safe in patients with cystic fibrosis carrying a G551D mutation and moderately impaired lung function. The objective of this retrospective study was to assess efficacy and safety of ivacaftor in severely ill patients with at least one G551D mutation.

**Methods:** Data from 14 patients with a FEV<sub>1</sub> <40% predicted who received ivacaftor on a “named patient program” base in Germany were analyzed.

**Results:** One patient took ivacaftor at a lower than recommended dose due to abundant mucus and a feeling to “suffocate.” No additional severe adverse events were reported. One further patient stopped ivacaftor due to lung transplantation, one due to perceived poor effectiveness, one due to pregnancy, and one stopped standard therapy. The remaining patients took ivacaftor regularly and did not change other therapies. FEV<sub>1</sub> increased by more than 5 %predicted in 5 of the 14 patients from baseline (average FEV<sub>1</sub> during the year prior to ivacaftor). On average, FEV<sub>1</sub> increased significantly by  $5.2 \pm 5.6\%$ predicted ( $p < 0.01$ ). The relative improvement in FEV<sub>1</sub> was  $19.7 \pm 22.1\%$ .

**Conclusion:** Ivacaftor was effective in many patients with poor lung function. The response was, however, variable. Although the drug appeared safe for most of these patients, increased bronchial secretions may warrant intensified physiotherapy and intravenous antibiotic treatment when ivacaftor is initiated.

© 2013 European Cystic Fibrosis Society. Published by Elsevier B.V. All rights reserved.

**Keywords:** CFTR; FEV<sub>1</sub>; Mucus; Adults; VX-770

## 1. Introduction

Cystic fibrosis (CF) is a multi-organ disease with an autosomal recessive inheritance. Despite intensive treatment, life expectancy is reduced in most people with CF, and pulmonary disease contributes most to morbidity and mortality.

The genetic basis for CF is mutations in a gene on chromosome 7 which codes for a CF transmembrane regulator (CFTR) chloride channel. Some of these mutations lead to a gating defect of the CFTR protein located in the apical membrane of epithelial cells

☆ This study has been presented as poster at the 14. Deutsche Mukoviszidosekongress on November 18 and 19, 2012 in Würzburg. A respective abstract was published in the abstract book on page 72, which is available for download at: [http://muko.info/fileadmin/redaktion/DMT/Abstraktband-2012\\_final.pdf](http://muko.info/fileadmin/redaktion/DMT/Abstraktband-2012_final.pdf).

\* Corresponding author at: Universitäts-Kinderklinik, Josef-Schneider-Str. 2, 97080 Würzburg, Germany. Tel.: +49 931 201 27728; fax: +49 931 201 27242.

E-mail address: [hebestreit@uni-wuerzburg.de](mailto:hebestreit@uni-wuerzburg.de) (H. Hebestreit).

like in the airway epithelium. Ivacaftor is a molecule which can potentiate *CFTR* function in several mutant gating defects [1]. In people with CF and at least one G551D mutation, ivacaftor has shown strong positive effects on pulmonary function and body weight without severe adverse effects [2]. Based on these findings in patients with forced expiratory volume in 1 second (FEV<sub>1</sub>) between 40 and 90% and additional data from adults [3] and children [4], ivacaftor has been approved for treating people with CF and at least one G551D mutation 6 years and older in the United States early in January 2012 [5] and also in Europe in July 2012 [6]. The approvals are not restricted with respect to pulmonary function.

The data available so far might suggest a good efficacy of ivacaftor also in severe lung disease, i.e. FEV<sub>1</sub> <40%predicted. However, patients with CF and a poor FEV<sub>1</sub> were not assessed during the studies cited above. Furthermore, there are no safety data for patients with severe lung disease receiving the novel therapy.

On a “named patient program” base, from December 2011 on ivacaftor was available for severely ill patients with CF, a G551D mutation, and an FEV<sub>1</sub> <40%predicted in Germany. The objective of this retrospective study was to assess efficacy and safety of ivacaftor in this population.

## 2. Methods

During regular meetings of German CF center physicians and international conferences, CF centres in Germany caring for patients who received ivacaftor on a named patient program basis were identified. In September 2012 and April 2013, the centres were asked to provide anonymous retrospective information on all patients who were treated with ivacaftor within the named patient program. The study was approved by the Ethics Committee of the Medical Faculty in Wuerzburg/Germany (Reference number 77/12).

The data provided by the centres included descriptive data, anthropometric information, pulmonary function measures,

blood chemistry, history of exacerbations, adverse events and reported experience of the patients.

### 2.1. Data analysis

Pulmonary function data and lung volumes submitted in liters were expressed in %predicted [7,8]. For each patient, data were plotted to visualize the individual changes over time for the 400-days period before starting ivacaftor and the period until ivacaftor was stopped for the first time or until no further follow-up data were available. Changes in FEV<sub>1</sub> (%predicted), RV/TLC (%predicted) and body weight (kg) were calculated for all patients. Since some patients had large variation in pulmonary function prior to the start of ivacaftor, individual baselines were calculated for each patient as average of all available data points from that patient collected during the year prior to the start of ivacaftor. The last measurement from each individual was used to calculate the changes. Baseline data were compared to the last measurement using paired *t*-tests. Statistically significant changes were assumed at *p* < 0.05.

## 3. Results

In total, data of 14 patients became available who received ivacaftor on a named patient basis in Germany. Patients' characteristics at the first day of treatment with ivacaftor are summarized in Table 1.

Patient 7 received ivacaftor only for about 8 weeks. Then he underwent lung transplantation and died shortly thereafter. Patient 10 stopped ivacaftor after about 4 months of treatment because no effect was observed. She died from advanced liver disease 2 months later. During the treatment with ivacaftor, there was no elevation in AST, ALT or bilirubin, and prothrombin time remained stable but prolonged around 22 s (international normalized ratio: 1.7 to 1.8). Patient 12 developed a severe exacerbation after starting ivacaftor requiring hospitalization. He had problems to expectorate the mucus from his bronchi which was liquefied by

Table 1  
Patients' characteristics at the first day of ivacaftor.

ID	Gender	Age (years)	Colonization	CFRD	Weight (kg)	Height (cm)	BMI (kg/m <sup>2</sup> )	FEV <sub>1</sub> (%predicted)	FVC (%predicted)	RV/TLC (%predicted)
1	Male	33	SA	No	46	168	16.3	26.9	52.4	244
2	Female	21	PSA	Yes	40	160	16.0	24.4	40.6	284
3	Male	23	PSA	No	43	172	14.5	18.7	33.5	330
4	Female	36	PSA	Yes	60	163	22.6	19.3	38.2	n.a.
5	Female	31	PSA, SA, ASP	No	52	160	20.3	27.6	57.4	n.a.
6	Male	30	PSA	No	67	162	25.5	33.4	58.1	n.a.
7	Male	41	PSA	No	71	180	21.9	17.7	52.5	n.a.
8	Male	31	PSA, SA	No	70	179	21.8	26.4	60.6	n.a.
9	Male	38	PSA, SA	No	54	169	18.9	17.8	29.8	273
10	Female	48	PSA	Yes	48	161	18.5	25.6	75.0	150
11	Female	41	PSA	Yes	63	164	23.4	21.6	69.3	173
12	Male	47	PSA	Yes	64	178	20.2	13.9	38.0	232
13	Female	36	PSA	Yes	54	179	16.9	38.7	83.5	214
14	Female	23	PSA	No	50	153	21.4	37.3	59.6	187
Average (±SD)		34 ± 8			56 ± 10	168 ± 9	19.9 ± 3.2	25.0 ± 7.5	53.5 ± 16.0	232 ± 58

SD — standard deviation; SA — *Staphylococcus aureus*; PSA — *Pseudomonas aeruginosa*; ASP — *Aspergillus fumigatus*; CFRD — cystic fibrosis-related diabetes mellitus; n.a. — not available.

ivacaftor so that he first reduced the dose and then stopped the drug after about 4 months of irregular intake. He subsequently died from pulmonary disease. Patient 13 became pregnant despite detailed written and oral information including signed consent (by her and her husband) while on ivacaftor and had to stop the treatment after 6 weeks. However, ivacaftor was restarted 2 weeks prior to delivery since the pulmonary situation of the patient became critical. The baby is apparently healthy so far. Patient 14 discontinued all standard treatment while on ivacaftor. She was lost from follow-up after 8 weeks of ivacaftor treatment. All other patients were on regular ivacaftor therapy until April 2013.

Mean follow-up time after the start of ivacaftor in the entire group was 235 days (42–395 days).

Fig. 1 depicts individual FEV<sub>1</sub> and body weight courses before and after starting ivacaftor. FEV<sub>1</sub> increased by more than 5 %predicted in 5 of the 14 patients. On average, a significant increase from baseline to the last day of follow-up on ivacaftor was observed ( $5.2 \pm 5.6$  %predicted; median 3.9; range –4.1 to 16.8 %predicted,  $p = 0.005$ ). The relative change in FEV<sub>1</sub> was  $19.7 \pm 22.1$  % (median 14.3; range –25.2 to 58.3%). Body weight increased in 7 of the 14 patients by more than 1 kg. The increase in body weight averaged  $2.1 \pm 2.4$  kg (median 1.1, range –0.3 to 6.3 kg,  $p = 0.005$ ). Residual volume divided by total lung capacity (RV/TLC) was only available in 10 patients. In these patients, RV/TLC decreased non-significantly by  $12.2 \pm 30.7$  %predicted.

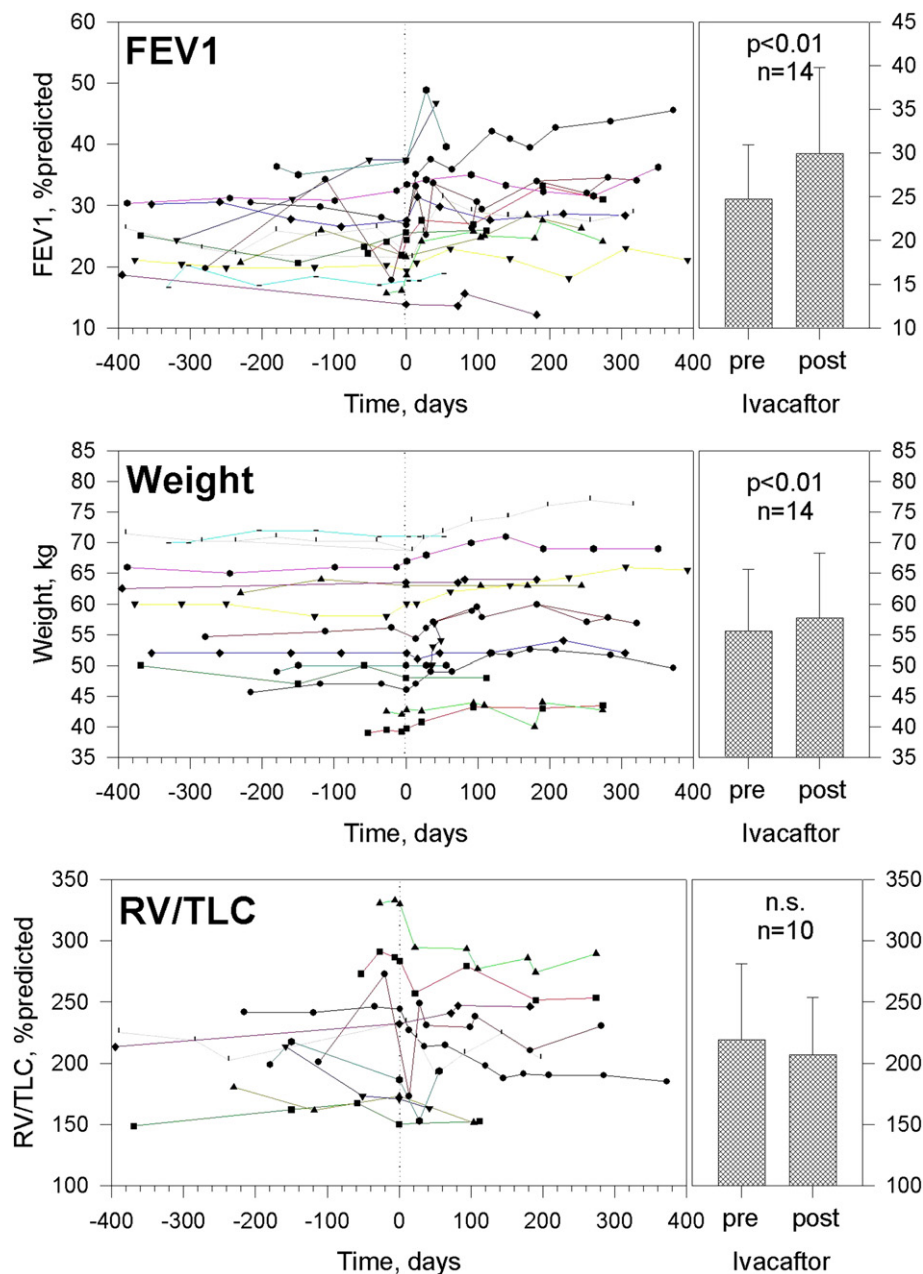


Fig. 1. Change in FEV<sub>1</sub>, body weight and RV/TLC in 14 patients after the start of ivacaftor (day 0). The graphs on the right display the average of all available measurements obtained during the year prior to ivacaftor ("pre") and the last measurement reported ("post").

The change in FEV<sub>1</sub> could not be predicted from baseline FEV<sub>1</sub> (Fig. 2) or baseline RV/TLC (data not shown). There also was no significant association between the changes in body weight and FEV<sub>1</sub>. However, a reduction in RV/TLC was significantly correlated with an increase in FEV<sub>1</sub> (Fig. 2).

### 3.1. Adverse events possibly associated with ivacaftor treatment

Three patients observed more secretions at the beginning of the ivacaftor treatment, both in the bronchi and the nasal cavity. One of these, patient 12, reported to “suffocate” from the secretions so that an unscheduled intravenous antibiotic therapy was initiated. Ultimately, the ivacaftor therapy had to be discontinued. With time, the other two patients observed a decrease in secretions. One additional patient complained about headache at the start of ivacaftor which resolved with time. In one patient, abdominal pain and worsening of pre-existing restless legs were reported. One patient experienced an intermittent increase in serum bilirubin just slightly above normal and another patient an intermittent increase in liver enzymes (maximal AST <3 times the upper limit of normal, maximal ALT <4 times the upper limit of normal) shortly after the initiation of ivacaftor. Ivacaftor was continued and AST and ALT normalized within 2 months. Except for the patient who had to stop ivacaftor due to abundant secretions, no unscheduled antibiotic therapy became necessary in any of the other 13 patients after the start of ivacaftor.

### 3.2. Patients' impressions on the effects of ivacaftor

All 14 patients reported their impressions after starting ivacaftor. Eight patients observed a better fitness shortly after starting ivacaftor, five a reduction in secretions compared with baseline and one an improved nasal breathing. Two patients could reduce their pancreatic enzyme supplementation.

## 4. Discussion

In patients with severe lung disease carrying the G551D mutation, ivacaftor induced a similar relative increase in FEV<sub>1</sub> from baseline – on average 19.7% – to the improvements

reported for patients with milder lung disease (17.2%; [2]). However, the increase in FEV<sub>1</sub> expressed in absolute percent of predicted was only about 5.2% in our severely affected patients and thus much lower than the 10.6% observed in patients with an FEV<sub>1</sub> between 40% and 90% predicted [2] or the nearly 10% shown for patients with an FEV<sub>1</sub> between 40% and 50% predicted (supplemental appendix to Ref. [2]).

There are also some preliminary data on the effects of ivacaftor in patients with a FEV<sub>1</sub> <40% for comparison with our findings. A case report of an adult patient with a FEV<sub>1</sub> of 24 %predicted demonstrates that considerable improvement in FEV<sub>1</sub> is possible with ivacaftor [10]. Furthermore, eight patients who participated in the controlled phase III trial on ivacaftor as controls [2] and rolled over to the open label PERSIST study, had a FEV<sub>1</sub> of  $34.5 \pm 3.7$  %predicted at the time they first received ivacaftor [11]. These patients improved their FEV<sub>1</sub> within 12 weeks of ivacaftor by  $13.0 \pm 10.5$  %predicted and thus much more than the 14 patients in our series. However, our patients had a far lower FEV<sub>1</sub> at baseline (mean:  $25.0 \pm 7.5$  %predicted). It is, therefore, likely that severe lung damage may limit the improvement in FEV<sub>1</sub> associated with ivacaftor. However, in our sample, FEV<sub>1</sub> or RV/TLC at baseline, expressed in percentage of predicted, could not predict the improvement in FEV<sub>1</sub> following the introduction of ivacaftor to the patients' medication. Nevertheless, a reduction in RV/TLC with ivacaftor was associated with an improvement in FEV<sub>1</sub> indicating that the effect of ivacaftor on FEV<sub>1</sub> may – at least in part – be mediated by effects on hyperinflation.

The weight gain following the start of ivacaftor treatment ( $2.1 \pm 2.4$  kg) compared similarly to the case series reported by Ramsey et al. (3.1 kg) [2], especially when differences between the populations (pure adult vs. mixed adolescent and adult) are taken into consideration.

There were several mainly non-serious adverse events associated with ivacaftor treatment in our case series and similar to those reported from the phase III trial (supplementary appendix to Ref. [2]). However, the patient with the lowest FEV<sub>1</sub> of about 14% predicted experienced major difficulties to clear the secretions from the airways so that the dose of ivacaftor had to be reduced and – later on – the drug had to be stopped. This

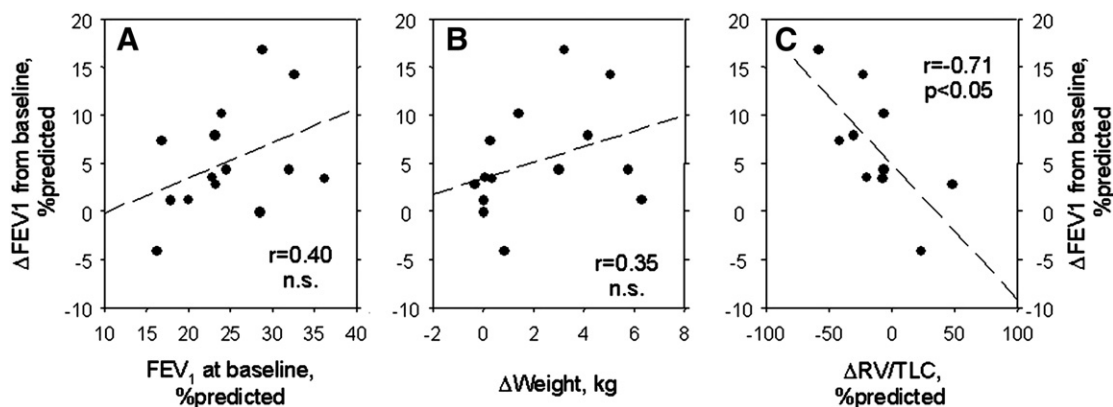


Fig. 2. Changes in FEV<sub>1</sub> after the start of ivacaftor and its associates. A) There was no association between baseline FEV<sub>1</sub> and  $\Delta\text{FEV}_1$ . B) The change in body weight was not significantly correlated with  $\Delta\text{FEV}_1$ . C) A decrease in RV/TLC was significantly associated with an increase in FEV<sub>1</sub> in the 10 patients with RV and TLC measurements.



observation is in line with the thoughts of Shah et al. [9] that liquification of sputum in people with very severe lung disease may lead to clinical deterioration. Based on the early experience with the above patient, some subsequent patients with severe lung disease were hospitalized for intravenous antibiotic treatment and intense physiotherapy prior to ivacaftor and for the first week after the drug was started.

This study has several limitations. First, the retrospective data collection does not allow for complete data with assessments at certain time points. Furthermore, there is no “placebo” control group. It may be speculated that the excitement associated with the novel treatment could have stimulated a better adherence to the other therapies, thereby leading to improvements in FEV<sub>1</sub> and weight gain. However, our patients had severely impaired pulmonary function so that treatment adherence was likely quite good even before the start of ivacaftor. In addition, a possible “placebo” effect is expected to wane with time. Our follow-up data over up to 13 months show that the effects of ivacaftor were not lost with time. In some patients, there was even a continuing improvement in FEV<sub>1</sub> over several months. Last but not least, the number of patients for analyses in this study is limited so that the average responses reported are susceptible to outliers. However, to our knowledge we included all patients participating in the named patient program in Germany and present the largest case series on the effects of ivacaftor in severely ill patients so far.

In conclusion, ivacaftor was effective in improving FEV<sub>1</sub> and body weight in patients with poor lung function although response was variable and absolute increase in FEV<sub>1</sub> was lower than reported in patients with better preserved lung function. Although the drug appears safe for most of the severely ill patients, increased bronchial secretions may warrant increased physiotherapy and intravenous antibiotic treatment in these patients when ivacaftor is initiated.

### Conflict of interest statement

H.H. received reimbursement for work in the VERTEX study VX08-770-102 and an honorarium for a presentation and his participation at the VERTEX advisory board meeting in Frankfurt/Germany on June 22, 2012 and April 12, 2013. J.G.M. received reimbursement for the work within VERTEX

studies VX08-770-102/-103/-105 and -661 and he participated in the VERTEX advisory board meetings in Amsterdam/Netherlands and Frankfurt/Germany in 2012 and 2013. R.F. participated in the VERTEX advisory board meetings in Amsterdam/Netherlands and Frankfurt/Germany in 2012 and 2013.

### References

- [1] Yu H, Burton B, Huang CJ, Worley J, Cao D, Johnson Jr JP, et al. Ivacaftor potentiation of multiple CFTR channels with gating mutations. *J Cyst Fibros* 2012;11:237–45.
- [2] Ramsey BW, Davies J, McElvaney NG, Tullis E, Bell SC, Dřevinec P, et al. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. *N Engl J Med* 2011;365:1663–72.
- [3] Accurso FJ, Rowe SM, Clancy JP, Boyle MP, Dunitz JM, Durie PR, et al. Effect of VX-770 in persons with cystic fibrosis and the G551D-CFTR mutation. *N Engl J Med* 2010;363:1991–2003.
- [4] Davies JC, Wainwright CE, Canny GJ, Chilvers MA, Howenstine MS, Munck A, et al. Efficacy and safety of ivacaftor in patients aged 6 to 11 years with cystic fibrosis with a G551D mutation. *Am J Respir Crit Care Med* Apr 3 2013 [Epub ahead of print].
- [5] U.S. Food and Drug Administration News Release. <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm289633.htm>; January 31 2012.
- [6] European Medicines Agency. EPAR summary for the public: Kalydeco. EMA/349471/2012 [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Summary\\_for\\_the\\_public/human/002494/WC500130744.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/002494/WC500130744.pdf).
- [7] Sherrill DL, Lebowitz MD, Knudson RJ, Burrows B. Continuous longitudinal regression equations for pulmonary function measures. *Eur Respir J* 1992;5:452–62.
- [8] Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault J-C. Lung volumes and forced ventilatory flows. *Eur Respir J* 1993;16: 5–40 [Suppl.].
- [9] Shah PI, Bush A, Canny GJ, Colin AA, Fuchs HJ, Geddes DM, et al. Recombinant human DNase I in cystic fibrosis patients with severe pulmonary disease: a short-term, double-blind study followed by six months open-label treatment. *Eur Respir J* 1995;8:954–8.
- [10] Polenakovik HM, Sanville B. The use of ivacaftor in an adult with severe lung disease due to cystic fibrosis ( $\Delta$ F508/G551D). *J Cyst Fibros* Jan 9 2013. <http://dx.doi.org/10.1016/j.jcf.2012.12.004> [pii: S1569-1993(12) 00237-8, Epub ahead of print].
- [11] McKone E, Li H, Davies JC, on behalf of the VX08-770-105 Study Group. Long-term safety and efficacy of ivacaftor in subjects with cystic fibrosis who have the G551D-CFTR mutation (abstract). *J Cyst Fibros* 2012;11(Suppl. 1):S13.